Best Available Copy

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/938,154	04/03/91	HARPOLD	M 51247

EXAMINER	
ULM, J	

18N2/0425

ART UNIT	PAPER NUMBER
1812	15

STEPHEN E. REITER
PRETTY, SCHROEDER, BRUEGGEMANN & CLARK
444 SOUTH FLOWER STREET - SUITE 2000
LOS ANGELES, CALIFORNIA 90071

DATE MAILED: 04/25/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 02/03/95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 53 to 63, 66 to 68, 70 to 75 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 64, 65 and 69 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 53 to 63, 66 to 68, 70 to 75 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1) Claims 53 to 63, 66 to 68 and 70 to 75 are pending in the instant application. Claims 53, 57, 58, 62 and 68 have been amended, claims 64, 65 and 69 have been canceled and claims 73 to 75 have been added as requested by Applicant in Paper Number 14.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2) Claims 58 and 68 stand objected to because they each recite an improper Markush group. Specifically, these claims do not clearly identify a Markush element. Claim 58 lists a Markush group composed of three members but does not identify the element that is to be provided by one of these elements. This claim should probable refer to "said nucleic acid comprising a sequence of nucleotides selected from the group consisting of". Similarly, claim 68 lists a Markush group composed of three members but also fails to identify the element that is to be provided by any one of those members. See M.P.E.P. 706.03(y).

3) Claims 53 to 63, 66 to 68 and 70 to 75 stand rejected under 35 U.S.C. § 112, first paragraph, because the instant specification is only enabling for those DNAs contained within the clones identified by the ATCC accession numbers presented on page 19 of the instant specification. These claims currently encompass any and all nucleic acids which can encode any and all human neuronal nicotinic acetylcholine receptor alpha and beta subunits, including mutants and derivatives thereof. However, the instant specification does not identify those amino acid

residues in the amino acid sequence of a human neuronal nicotinic acetylcholine receptor subunit which are essential for biological activity and structural integrity and those residues which are either expendable or substitutable. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of over 400 amino acid residues before they could even begin to rationally design a functional human neuronal nicotinic acetylcholine receptor subunit having other than a natural amino acid sequence. The disclosure of only partial DNA sequences encoding human neuronal nicotinic acetylcholine receptor subunits with natural but undetermined amino acid sequences is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass any and all human neuronal nicotinic acetylcholine receptor subunits, including mutants thereof, which are encoded by a DNA which hybridizes to one of the disclosed DNAs under high stringency conditions.

The current claim limitations are directly analogous to those of claim 7 of U.S. Patent Number 4,703,008 which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 18 U.S.P.Q. 2d, 1016 (see page 1026, section D). In that instance, nucleic acid hybridization and a biological activity of the encoded protein, erythropoietin (EPO), were the sole limitations

of a contested claim. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes DNAs encoding three naturally occurring human neuronal nicotinic acetylcholine receptor subunits, it does not describe even a single variant thereof. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify the grant of the claims sought. As indicated, the instant specification is even more limited than the '008 patent because it describes only natural proteins and no analogs or mutants thereof and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

Applicant's arguments in traversal of this rejection that were presented in Paper Number 14 do not take into consideration the actual breadth of these claims as discussed above. Additionally, Applicant's argument that the preparation and screening of DNA clones therefrom are basic skills commonly utilized by persons of ordinary skill in the art is in conflict with the holding in Amgen Inc. v. Chugai that the conception of a generalized approach for screening a DNA library that might be

used to identify and clone a DNA encoding a particular protein of unknown constitution is not conception of a substantially pure nucleic acid encoding that protein, since it is not a definite and permanent idea of the complete and operative invention. In effect, the conception of an isolated DNA encoding a particular protein does not occur until that DNA has actually been isolated and the only isolated DNAs that are described in the instant specification are contained in the ATCC deposits which are identified on page 19 of the instant specification.

4) The specification stands objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the production of a substantially pure subunit of a human neuronal nicotinic acetylcholine receptor. Applicant has urged that, once given an expression vector encoding a protein, it is within the routine skill of a practitioner of the art to produce and purify the protein encoded thereby. Whereas the routine nature of the production of such a protein is conceded, the recovery and purification of that protein from the host in which it is produced is not a routine practice. The receptor subunits of the instant invention are membrane proteins having four putative transmembrane domains. Such proteins would be as difficult to recover from a heterologous host as they would from the cells in which they are naturally produced. If the recovery of a recombinantly produced receptor subunit of the instant invention is routine, as Applicant has alleged, then Applicant

should be able to readily identify a reference which described the recovery of a structurally related protein from a heterologous host prior to the filing of the instant application. It is clear from the art of record that a number of recombinant DNAs encoding ligand-gated ion channel subunits which are structurally and functionally related to those of the instant invention were known in the art by that time.

5) Claims 53, 54, 57 to 63, 66 to 68, 70 and 72 to 75 are rejected under 35 U.S.C. § 103 as being unpatentable over the Boulter et al. publication in view of the Grenningloh et al., Schofield et al. and Noda et al. publications for those reasons of record in Paper Number 12. Applicant's reliance upon the decision in Amgen Inc. v. Chugai in the traversal of this rejection is not persuasive. The finding in that decision that, as of 1983, an artisan did not have a reasonable expectation of isolating a DNA encoding EPO from a human genomic DNA library by probing that library with a cDNA encoding monkey EPO is not in conflict with the standing rejection. In the instant rejection the Grenningloh et al., Schofield et al. and Noda et al. publications provide two elements. These references show that the isolation of a cDNA encoding a human ligand-gated ion channel subunit from an appropriate human cDNA library by probing that library with a DNA encoding a ligand-gated ion channel subunit from a different mammal was a routine practice in the art of molecular biology as of 1990. These references further show that

the sequences of the genes encoding different members of this receptor subunit superfamily were known to be highly conserved between homologous receptor subunits from different mammalian species such as rats, cows and humans at the time that the instant invention was made. This combination of references effectively shows that an artisan had more than a reasonable expectation that a cDNA encoding a particular human ligand-gated ion channel subunit could have been isolated by probing a human cDNA library with a DNA encoding a homologous receptor from a different mammal, as required to support a rejection under 35 U.S.C. § 103. Applicant has not identified an error in this showing

Applicant has suggested that this rejection is directed to a process of making the invention rather than the product claimed. It is noted as a matter of law that a product can not be held to be obvious unless a method of making that product was also in the hands of an artisan at the time that it was made. This rejection, therefore, must address not only the claimed nucleic acid but also its method of making. It is further noted that the prior art does not have to disclose or suggest each and every feature of a product prior to its making so long as those features are comparable to analogous products that were known in the prior art (In re Dillon, 16 USPQ2d 1897, In re Wright, 6 USPQ2d 1959). A DNA encoding a human acetylcholine receptor subunit of the instant invention does not differ from those DNAs

encoding the rat acetylcholine receptor subunits of Boulter et al. publication in any unexpected manner as shown by the sequence comparisons presented in Figures 7, 8 and 9 of the instant specification. This position is further supported by the data presented in Table I of the declaration by Edwin C. Johnson under 37 C.F.R. § 1.132 which shows that the rat neuronal nicotinic receptors of Boulter et al. and the human neuronal nicotinic receptors of the instant invention have virtually identical relative binding affinities for three of four ligands tested. These receptors only differ in their affinities for nicotine. Since nicotine is not a naturally encountered neurotransmitter an artisan would not have expected receptor affinity for this ligand to be necessarily conserved between species. Additionally, an artisan would not have expected these receptor subunits to be identical, only structurally and functionally homologous, which they are.

The declaration by Edwin C. Johnson under 37 C.F.R. § 1.132 states that the receptor subunits that were described in the Grenningloh et al., Schofield et al. and Noda et al. publications are not functionally related to the receptor subunits of the instant invention. It is unclear upon what basis this statement has been made since all of these subunits were known to belong to the super family of ligand-gated ion channel receptor subunits. Members of this super family were all known to be functionally and structurally related as indicated by the text in the first

and second paragraphs of the Grenningloh et al. publication. Since these are the only members of this receptor subunit superfamily for which human sequence information was available, an artisan would have relied upon the disclosed similarities between these subunits and their homologues from other mammalian species as predictive of the sequence similarity to be expected between the rat subunits of Boulter et al. and their human counterparts. The declaration by Edwin C. Johnson alleges that there are instances wherein inter-species subunits are neither predictive of, nor are suitable paradigms for purposes of analogy or comparison to other receptors from the same family. It is noted, however, that no reference has been cited or made of record which reported less than 95% amino acid sequence identity between homologous receptor subunits from different mammalian species prior to the making of the instant invention.

The Grenningloh et al., Schofield et al. and Noda et al. publications were not chosen from a plurality of related publications simply to support this rejection. They were chosen because they were the only references of record which described isolated DNAs encoding human ligand-gated ion channel subunits. Therefore, all of the relevant art that was available to an artisan at the time that the instant invention was made taught that those genes and the receptor subunits encoded thereby that were most closely related to the rat neuronal nicotinic receptors of Boulter et al. in structure and function were known to be

highly conserved between mammalian species. Based upon this teaching, an artisan of molecular biology would have reasonably predicted that a DNA encoding a human homologue of any of the rat neuronal nicotinic receptor subunits of Boulter et al. would have had sufficient sequence similarity to have permitted its isolation by those cDNA isolations methods that were disclosed in any of the Grenningloh et al., Schofield et al. and Noda et al. publications at the time of the instant invention.

6) Applicant's arguments filed 03 February of 1995 have been fully considered but they are not deemed to be persuasive.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm at telephone number (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

Best Available Copy

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, G. D. Draper can be reached on (703) 308-4232. The fax phone number for this group is (708) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. D. U.

John D. Ulm

Stephen Walsh

STEPHEN G. WALSH
PRIMARY EXAMINER
GROUP 1800